PHARMACOLOGY AND TOXICOLOGY

Distribution of Ethomerzol in Organ and Tissue of Rats after Single and Course Treatment

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 145, No. 1, pp. 47-49, January, 2008
Original article submitted September 20, 2007.

We studied experimental kinetics of ethomerzol (5-ethoxy-2ethylthiobenzimidazole hydrochloride) distribution in the liver, brain, kidneys, spleen, heart, skeletal muscles, lungs, adipose tissue, and testes of rats after its single or course administration. Peculiarities of ethomerzol distribution in various administration regimens were analyzed. Single treatment led to more pronounced accumulation of the drug in the liver. Study of ethomerzol distribution after course treatment revealed organs and tissues accumulating the drug (blood, brain, heart, kidneys, lungs, and adipose tissue).

Key Words: *ethomerzol; 5-ethoxy-2ethylthiobenzimidazole hydrochloride; pharmacokinetics; distribution*

The main pharmacological effect of ethomerzol (5-ethoxy-2ethylthiobenzimidazole hydrochloride) is improvement of organism's resistance to hypoxic exposures of all types. The drug is effective in disturbances of cerebral and mesenterial circulation, heart ischemia, hemorrhagic shock. Ethomerzol is effective in the rehabilitation period after intoxication.

Experimental basis for pharmacological characteristics of any drug and substance is evaluation of the dynamics of its concentrations in tissues, organs, and biological fluids. Pharmacokinetics of drugs, benzimidazole derivatives, is characterized by high intensity of their distribution from the blood into organs and tissues [1,2,7].

Here we studied ethomerzol distribution in rat organs and tissues after different regimens of its administration.

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MATERIALS AND METHODS

Experiments were carried out on mongrel albino male rats weighing 200-250 g. The animals were maintained on a full-value ration with free access to water and under natural illumination. Ethomerzol was administered intragastrically in a dose of 100 mg/kg once or daily for 14 days (course treatment). One hour after single or last dose of the drug, the rats were decapitated and the content of the drug in the whole blood, plasma, erythrocytes, liver, brain, kidneys, spleen heart, skeletal muscles, lungs, adipose tissue, and testes was measured. The concentration of ethomerzol was measured on a gas chromatograph (model 3700) with an electron capture detector containing ^{63}Ni-β-ionization source using a 2-m glass column (internal diameter 2.5 mm). Chromatro N-Super with 3% liquid phase SE-30 was used as the sorbent.

The data were processed statistically using Statistica 6.0 software. Means (M) and errors of the mean (m) were calculated.

0007-4888/08/1451-0041

RESULTS

After single peroral administration of ethomerzol to rats, its concentrations in the whole blood, plasma, and erythrocytes were 6.33±0.33, 4.22±0.23, and 7.13±0.37 μg/ml, respectively. Erythrocytes selectively accumulated ethomerzol. The concentration of the drug in erythrocytes was by 1.69 times higher than in the plasma (Table 1). After course treatment, the concentrations of ethomerzol in the whole blood, plasma, and erythrocytes increased by 3.11, 3.3, and 1.42 times respectively.

After single and course treatment, ethomerzol was detected in all studied organs and tissues; considerable heterogeneity of its distribution was observed.

Ethomerzol rapidly accumulated in the liver tissue. One hour after single administration of ethomerzol, its concentration in the liver surpassed its concentration in the whole blood and plasma by 11.96 and 17.93 times, respectively (Table 1). Study of the kinetics of ethomerzol concentration in rat liver confirmed high extraction capacity of this tissue for this preparation, which is typical of benzimidazole derivatives [1]. Imidazoles, in particular, benzimidazoles, are excreted with the bile and their presence in the organism is prolonged due to enterohepatic recirculation [1].

After course administration of ethomerzol, its concentration in the liver was lower than after single administration by 1.1 times, the tissue—whole blood and tissue—plasma distribution coefficients (k_p1 and k_p2) decreased by 3.47 and 3.67 times, respectively (Table 1). After course administration of the drug, the distribution coefficients for all other studied organs (brain, skeletal muscles, heart, kidneys, lungs, adipose tissue, spleen, and testes) did not considerably change (Table 1). These findings suggest that the decrease in ethomerzol concentration in the liver after course administration of the drug is not related to its redistribution between other organs and tissues, but results from its enhanced elimination from the liver due to intensification of biotransformation processes.

Permeability of the blood-brain barrier for imidazoles depends on their physicochemical properties determined by chemical structure of radicals in the benzimidazole cycle.

One hour after single administration of ethomerzol, its concentration in the brain surpassed its parallel concentration in the whole blood and plasma by 3.42 and 5.13 times, respectively (Table). Long-term treatment with ethomerzol was associated with a 4.46-fold increase in its concentration in the brain, but k_p1 and k_p2 for the brain increased insignificantly (by 1.43 and 1.35 times) due to the increase in its concentrations in the whole blood and plasma.

One hour after single administration of ethomerzol, its concentration in the kidneys was lower than in the whole blood and plasma (k_p1=0.55; k_p2=0.83), while after course treatment we observed accumulation of the drug in the kidney tissue: k_p1 increased by 50.9% and k_p2 by 42.17% (Table 1).

After single administration ethomerzol was detected in skeletal muscles (k_p1=0.72, k_p2=1.08).

TABLE 1. Concentration of Ethomerzol in Rats after Single and Course Treatment (n=5; $M±m$)

Organ, tissue	Single treatment			Course treatment		
	C, ng/g (ml)	k_p1	k_p2	C, ng/g (ml)	k_p1	k_p2
Whole blood	6327.27±328.28	—	—	19 730.18±1345.12	—	—
Plasma	4218.18±230.1	—	—	13 928.31±720.0	—	—
Erythrocytes	7128.72±371.35	—	1.69	10 092.98±540.0	—	1.38
Liver	75 645.55±3841.48	11.96	17.93	68 165.12±4779.15	3.45	4.89
Brain	21 660.37±1863.44	3.42	5.13	96 686.1±8739.22	4.9	6.94
Skeletal muscles	4576.33±264.1	0.72	1.08	13 948.45±1373.67	0.71	1.0
Heart	2739.57±253.78	0.43	0.65	11 570.25±570.06	0.59	0.8
Kidney	3483.3±294.33	0.55	0.83	16 461.32±971.32	0.83	1.18
Lungs	3973.57±335.31	0.63	0.94	15 220.67±2171.63	0.77	1.09
Adipose tissue	8029.32±688.96	1.27	1.9	26 996.62±3099.62	1.37	1.94
Spleen	8781.58±893.94	1.39	2.08	19 995.37±1567.45	1.01	1.44
Testes	949.78±80.84	0.15	0.22	1988.72±82.64	0.1	0.14

Note. C: concentration of ethomerzol.

The distribution coefficients for skeletal muscles in different treatment regimens were similar, *i.e.* the concentration of ethomerzol in skeletal muscles changed with the same rate as in the blood.

The concentration of ethomerzol in the heart 1 h after single administration was slightly below its level in the whole blood and plasma: k_p1=0.43 and k_p2=0.65. Course treatment led to accumulation of ethomerzol in the heart: k_p1 increased by 37.21% and k_p2 by 23.08% (Table 1).

The concentration of ethomerzol in the lungs 1 h after single administration was below its simultaneous concentration in the whole blood and plasma (k_p1=0.63, k_p2=0.94). Course treatment led to accumulation of ethomerzol in the lungs: k_p1 increased by 22.22% and k_p2 by 15.96% (Table 1).

Ethomerzol was detected in the adipose tissue: one hour after single administration its concentration in the adipose tissue surpassed its concentration in the whole blood and plasma by 1.27 and 1.9 times, respectively (Table 1). Course treatment was associated with minor accumulation of ethomerzol in the adipose tissue: k_p1 increased by 7.9% and k_p2 by 2.1%.

Ethomerzol intensively distributed from the blood into the spleen: one hour after single administration its concentration in the spleen surpassed its concentration in the whole blood and plasma by 1.39 and 2.08 times, respectively. Long-term treatment with ethomerzol was associated with a 2.28-fold increase in its concentration in the spleen, but k_p1 and k_p2 decreased by 27.34% and 30.77%, respectively, because the increase in plasma concentration of ethomerzol in the whole blood and plasma was more pronounced (by 3.12 and 3.3 times, respectively).

The concentration of ethomerzol in the testes 1 h after single administration was below its level in the whole blood and plasma (k_p1=0.15, k_p2=0.22). Course treatment with ethomerzol was associated with acceleration of its elimination from the testes: k_p1 decreased by 33.3% and k_p2 by 36.4% (Table 1).

Thus, experimental data suggest that ethomerzol in various treatment regimes is intensively transported from the blood into organs and tissues. Study of ethomerzol distribution after course treatment revealed organs and tissues accumulating the drug (blood, brain, heart, kidneys, lungs, and adipose tissue). Our data on ethomerzol distribution confirm the results obtained in similar studies of the pharmacokinetics of imidazoles, in particular, benzimidazole derivatives [1,7].

REFERENCES

1. A. A. Spasov, L. A. Smirnova, I. N. Iezhitsa, *et al., Vopr. Med. Khimii*, **48**, No. 3, 233-258 (2002).
2. F. C. Cheng, Y. E. Ho, L. C. Hung, *et al. J. Chromatogr. A*, **949**, Nos. 1-2, 35-42 (2002).
3. M. C. Ko, H. Wei, Y.H. Woods, and R.T. Kennedy, *J. Pharmacol. Exp. Ther.,* **318**, No. 3, 1257-1264 (2006).
4. M. Molimard, B. Diquet, and M. S. Benedetti, *Fundam. Clin. Pharmacol.*, Vol. **18**, No. 4, 399-411 (2004).
5. N. V. Nagaraja, S. K. Singht, J. K. Paliwal, and R. C. Gupta, *J. Pharm. Pharmacol*., **52**, No. 10, 1253-1263 (2000).
6. S. Sanchez, L. Alvarez, J. Sallovitz, and C. Lanusse, *J. Vet. Pharmacol. Ther*., **23**, No. 4, 193-201 (2000).
7. X. N. Zhang, Q. Zhang, H. Wen, *et al., Yao Xue Xue Bao*, **38**, No. 6, 462-463 (2003).